

**IN THE CLAIMS**

Please replace all prior versions, and listings, of claims in the application with the following list of claims:

1. (Withdrawn) The method of claim 188, wherein the act of identifying each of the one or more nucleotides comprises:

providing a sample comprising a plurality of aggregates of size of at least about 500 nm;

adsorbing at least some of the one or more nucleotides to at least some of the plurality of aggregates;

exposing the sample to electromagnetic radiation to cause surface-enhanced emission;  
obtaining spectral information of the sample, wherein at least one spectral line of the information represents a single nucleotide adsorbed on one of the plurality of aggregates; and  
determining the presence of the single nucleotide from the at least one spectral line.

2. (Withdrawn) A method as in claim 1, the exposing step comprising exposing the sample to electromagnetic radiation and causing Raman scattering of the sample, and the obtaining step comprising obtaining Raman information of the sample, wherein a single Raman line of the information represents the single nucleotide.

3. (Withdrawn) A method as in claim 1, wherein the sample is free of an emission-enhancing aid.

4. (Withdrawn) A method as in claim 1, wherein the spectral information is a surface-enhanced Raman spectrum, having an enhancement factor of at least about  $10^{10}$ .

5. (Withdrawn) A method as in claim 1, wherein each aggregate of the plurality of aggregates comprises a plurality of metal particles.

6. (Withdrawn) A method as in claim 5, wherein at least some of the metal particles are selected from the group consisting of silver, gold and copper particles.

7. (Withdrawn) A method as in claim 6, wherein the plurality of aggregates is formed in situ by exposure to the electromagnetic radiation.
8. (Withdrawn) A method as in claim 1, wherein the plurality of aggregates is selected from the group consisting of colloids suspended in a medium, aggregates deposited on a substrate and lithography-produced metal aggregates.
9. (Withdrawn) A method as in claim 8, wherein the medium is selected from the group consisting of water, an organic solvent and a gel.
10. (Withdrawn) A method as in claim 8, wherein the substrate is selected from the group consisting of an electrode, a glass layer and a quartz layer.
11. (Withdrawn) A method as in claim 1, wherein the sample consists essentially of a plurality of aggregates of from about 500 nm to about 20 microns in dimension.
12. (Withdrawn) A method as in claim 1, wherein the electromagnetic radiation is non-resonant radiation.
13. (Withdrawn) A method as in claim 12, wherein the electromagnetic radiation is near infrared radiation.
14. (Withdrawn) A method as in claim 1, wherein the spectral information is Raman information that defines less than a complete Raman spectrum.
15. (Withdrawn) A method as in claim 14, wherein the spectral information is less than 5 Raman lines.
16. (Withdrawn) A method as in claim 14, wherein the spectral information is less than 2 Raman lines.

17. (Withdrawn) A method as in claim 1, wherein the spectral information is a single Raman line.

18. (Cancelled)

19. (Withdrawn) A method as in claim 1, wherein the single nucleotide is selected from the group consisting of thymine, adenine, cytosine, guanine, and uracil.

20-22. (Cancelled)

23. (Withdrawn) The method of claim 188, wherein the act of identifying each of the one or more nucleotides comprises:

- providing a sample comprising a plurality of aggregates;
- adsorbing each of the one or more nucleotides to at least some of the plurality of aggregates, wherein at least one aggregate of the plurality of aggregates comprises a metal cluster of at least seven particles and adsorbs only one nucleotide;
- exposing the sample to electromagnetic radiation to cause surface-enhanced emission;
- obtaining spectral information of the sample, wherein the only one nucleotide contributes to the spectral information; and
- determining the presence of the only one nucleotide from the spectral information.

24. (Withdrawn) A method as in claim 23, the exposing step comprising exposing the sample to electromagnetic radiation to cause Raman scattering, and the obtaining step comprises obtaining a Raman spectrum of the sample, wherein the only one nucleotide contributes to at least one Raman signal of the Raman spectrum.

25. (Withdrawn) A method as in claim 23, wherein the plurality of aggregates comprises a metal cluster of at least ten particles.

26. (Withdrawn) A method as in claim 23, wherein the plurality of aggregates comprises a metal cluster of at least twenty particles.

27. (Withdrawn) A method as in claim 23, wherein the plurality of aggregates comprises a metal cluster of at least thirty-five particles.
28. (Withdrawn) A method as in claim 23, wherein the sample is free of an emission-enhancing aid.
29. (Withdrawn) A method as in claim 24, wherein the Raman spectrum is a surface-enhanced Raman spectrum, having an enhancement factor of at least  $10^{10}$ .
30. (Withdrawn) A method as in claim 23, wherein the metal cluster of at least seven particles comprises particles selected from the group consisting of silver, gold and copper particles.
31. (Withdrawn) A method as in claim 23, wherein the plurality of aggregates is formed in situ by exposure to the electromagnetic radiation.
32. (Withdrawn) A method as in claim 23, wherein the plurality of aggregates is selected from the group consisting of a colloids suspended in a medium, aggregates deposited on a substrate and lithography produced metal aggregates.
33. (Withdrawn) A method as in claim 32, wherein the medium is selected from the group consisting of water, an organic solvent and a gel.
34. (Withdrawn) A method as in claim 32, wherein the substrate is selected from the group consisting of an electrode, a glass layer and a quartz layer.
35. (Withdrawn) A method as in claim 23, wherein at least some of the aggregates have a dimension of at least about 500 nm.

36. (Withdrawn) A method as in claim 23, wherein the electromagnetic radiation is non-resonant radiation.

37. (Withdrawn) A method as in claim 36, wherein the electromagnetic radiation is near infrared radiation.

38. (Cancelled)

39. (Withdrawn) A method as in claim 23, wherein the only one nucleotide is selected from the group consisting of thymine, adenine, cytosine, guanine, and uracil.

40-42. (Cancelled)

43. (Withdrawn) A method as in claim 23, wherein the sample consists essentially of aggregates of size of from about 500 nm to about 20 microns.

44. (Withdrawn) A method as in claim 23, wherein the plurality of aggregates comprises a plurality of metal particles each having a dimension of no more than about 100 nm.

45. (Withdrawn) A method as in claim 23, wherein the plurality of aggregates comprises a plurality of metal particles each having a dimension of no more than about 75 nm.

46. (Withdrawn) The method of claim 188, wherein the act of identifying each of the one or more nucleotides comprises:

- providing a sample comprising a plurality of aggregates;
- adsorbing at least some of the one or more nucleotides to at least some of the plurality of aggregates, wherein each aggregate comprises a plurality of metal particles, each metal particle having a dimension of no more than about 100 nm and at least one aggregate adsorbs only one nucleotide;

- exposing the sample to electromagnetic radiation to cause surface-enhanced emission;
- obtaining spectral information of the sample, wherein the only one nucleotide

contributes to the spectral information; and

determining the presence of the only one nucleotide from the spectral information.

47. (Withdrawn) A method as in claim 46, wherein the exposing step comprises causing surface-enhanced emission and the obtaining step comprises obtaining Raman spectral information.

48. (Withdrawn) A method as in claim 46, wherein the sample is free of an emission-enhancing aid.

49. (Withdrawn) A method as in claim 46, wherein the spectral information is a surface-enhanced Raman spectrum, having an enhancement factor of at least  $10^{10}$ .

50. (Withdrawn) A method as in claim 46, wherein at least some of the metal particles are selected from the group consisting of silver, gold and copper particles.

51. (Withdrawn) A method as in claim 46, wherein the plurality of aggregates is formed in situ by exposure to the electromagnetic radiation.

52. (Withdrawn) A method as in claim 46, wherein the plurality of aggregates is selected from the group consisting of a colloids suspended in a medium, aggregates deposited on a substrate and lithography produced metal aggregates.

53. (Withdrawn) A method as in claim 52, wherein the medium is selected from the group consisting of water, an organic solvent and a gel.

54. (Withdrawn) A method as in claim 52, wherein the substrate is selected from the group consisting of an electrode, a glass layer and a quartz layer.

55. (Withdrawn) A method as in claim 46, each metal particle having a dimension of no more than about 75 nm.

56. (Withdrawn) A method as in claim 46, wherein the electromagnetic radiation is non-resonant radiation.

57. (Withdrawn) A method as in claim 56, wherein the electromagnetic radiation is near infrared radiation.

58. (Withdrawn) A method as in claim 46, wherein the spectral information consists essentially of less than 5 lines of a Raman spectrum.

59. (Cancelled)

60. (Withdrawn) A method as in claim 46, wherein the only one nucleotide is selected from the group consisting of thymine, adenine, cytosine, guanine, and uracil.

61-63. (Cancelled)

64. (Withdrawn) The method of claim 188, wherein the act of identifying each of the one or more nucleotides comprises:

providing a sample comprising a plurality of aggregates;  
to at least one aggregate, adsorbing only one nucleotide that is free of an emission-enhancing aid;  
exposing the sample to electromagnetic radiation; and  
obtaining a spectrum, wherein the only one nucleotide contributes to at least one signal of the spectrum.

65. (Withdrawn) A method as in claim 64, wherein the spectrum is a surface-enhanced Raman spectrum, having an enhancement factor of at least  $10^{10}$ .

66. (Withdrawn) A method as in claim 64, wherein each aggregate of the plurality of aggregates comprises a plurality of metal particles.

67. (Withdrawn) A method as in claim 66, wherein at least some of the metal particles are selected from the group consisting of silver, gold and copper particles.
68. (Withdrawn) A method as in claim 64, wherein the plurality of aggregates is formed in situ by exposure to the electromagnetic radiation.
69. (Withdrawn) A method as in claim 64, wherein the plurality of aggregates is selected from the group consisting of a colloids suspended in a medium, aggregates deposited on a substrate and lithography produced metal aggregates.
70. (Withdrawn) A method as in claim 69, wherein the medium is selected from the group consisting of water, an organic solvent and a gel.
71. (Withdrawn) A method as in claim 69, wherein the substrate is selected from the group consisting of an electrode, a glass layer and a quartz layer.
72. (Withdrawn) A method as in claim 64, wherein at least some of the aggregates have a dimension of at least about 500 nm.
73. (Cancelled)
74. (Withdrawn) A method as in claim 64, wherein the only one nucleotide is selected from the group consisting of thymine, adenine, cytosine, guanine, and uracil.
- 75-77. (Cancelled)
78. (Withdrawn) The method of claim 188, wherein the act of identifying each of the one or more nucleotides comprises:  
providing a sample comprising a plurality of surfaces;  
to a portion of the plurality of surfaces, adsorbing only one nucleotide; and



exposing the sample to electromagnetic radiation to cause the sample to emit radiation such that the sample is free of photobleaching.

79. (Withdrawn) A method as in claim 78, wherein the plurality of surfaces comprises a plurality of aggregates.

80. (Withdrawn) A method as in claim 79, wherein the plurality of aggregates comprises a plurality of metal particles.

81. (Withdrawn) A method as in claim 80, wherein at least some of the metal particles are selected from the group consisting of silver, gold and copper particles.

82. (Withdrawn) A method as in claim 79, wherein the plurality of aggregates is selected from the group consisting of a colloids suspended in a medium, aggregates deposited on a substrate and lithography produced metal aggregates.

83. (Withdrawn) A method as in claim 82, wherein the medium is selected from the group consisting of water, an organic solvent and a gel.

84. (Withdrawn) A method as in claim 82, wherein the substrate is selected from the group consisting of an electrode, a glass layer and a quartz layer.

85. (Withdrawn) A method as in claim 78, wherein the plurality of surfaces comprises a plurality of aggregates of metal particles, each of the metal particles having a dimension of no more than about 100 nm.

86. (Cancelled)

87. (Withdrawn) A method as in claim 78, wherein the only one nucleotide is selected from the group consisting of thymine, adenine, cytosine, guanine, and uracil.

88-90. (Cancelled)

91. (Withdrawn) The method of claim 188, wherein the act of identifying each of the one or more nucleotides comprises exposing each of the one or more nucleotides to electromagnetic radiation to cause Raman scattering, obtaining Raman spectral information, and determining the presence of each of the one or more nucleotides from at least one anti-Stokes line.

92. (Withdrawn) A method as in claim 91, wherein each of the one or more nucleotides is adsorbed on a plurality of surfaces.

93. (Withdrawn) A method as in claim 91, wherein at least one nucleotide is exposed to non-resonant radiation.

94. (Withdrawn) A method as in claim 91, wherein the electromagnetic radiation is near infrared radiation.

95. (Withdrawn) A method as in claim 94, wherein the near infrared radiation has a wavelength of at least 1000 nm.

96. (Withdrawn) The method of claim 188, wherein the act of identifying each of the one or more nucleotides comprises:

- allowing each of the one or more nucleotides to become surface-adsorbed;
- exposing each of the one or more nucleotides to electromagnetic radiation to cause surface-enhanced emission; and
- obtaining unique surface-enhanced spectral information attributed to each of the one or more nucleotides.

97. (Withdrawn) A method as in claim 96, wherein each of the one or more nucleotides is surface-adsorbed onto one of a plurality of surfaces.

98. (Withdrawn) A method as in claim 97, wherein the plurality of surfaces is included in a moving stream.

99. (Withdrawn) A method as in claim 97, wherein the surfaces is are surfaces of aggregates, the aggregates being selected from the group consisting of a plurality of aggregates suspended in a medium, a plurality of aggregates deposited on a substrate and lithography produced metal aggregates.

100. (Withdrawn) A method as in claim 99, wherein the plurality of aggregates comprise clusters of metal particles.

101. (Withdrawn) A method as in claim 100, wherein at least some of the metal particles are selected from the group consisting of silver, gold and copper particles.

102. (Withdrawn) A method as in claim 99, wherein the medium is selected from the group consisting of water, an organic solvent and a gel.

103. (Withdrawn) A method as in claim 100, wherein the substrate is selected from the group consisting of an electrode, a glass layer and a quartz layer.

104. (Withdrawn) A method as in claim 96, comprising allowing each of the one or more nucleotides to become surface-absorbed on a plurality of protrusions and voids on a rough metal film.

105. (Withdrawn) A method as in claim 96, wherein the electromagnetic radiation is non-resonant radiation.

106. (Withdrawn) A method as in claim 96, wherein the electromagnetic radiation is near infrared radiation.

107. (Withdrawn) The method of claim 188, wherein the act of identifying each of the one or more nucleotides comprises providing a plurality of aggregates, attaching each of the one or more nucleotides to one or more aggregates, exposing the plurality of aggregates to near infrared radiation, and inducing at least one electromagnetic resonance in the plurality of aggregates to cause a surface-enhanced radiation.

108. (Withdrawn) A method as in claim 107, wherein the near infrared radiation has a wavelength of at least 1000 nm.

109. (Withdrawn) A method as in claim 107, wherein the plurality of aggregates comprises a plurality of metal particles.

110. (Withdrawn) A method as in claim 109, wherein at least some of the metal particles are selected from the group consisting of silver, gold and copper particles.

111. (Withdrawn) A method as in claim 107, wherein the plurality of aggregates is formed in situ by exposure to the electromagnetic radiation.

112. (Withdrawn) A method as in claim 107, wherein the plurality of aggregates is selected from the group consisting of colloids suspended in a medium, aggregates deposited on a substrate and lithography produced metal aggregates.

113. (Withdrawn) A method as in claim 112, wherein the medium is selected from the group consisting of water, an organic solvent and a gel.

114. (Withdrawn) A method as in claim 112, wherein the substrate is selected from the group consisting of an electrode, a glass layer and a quartz layer.

115. (Withdrawn) A method as in claim 109, wherein each metal particle has a dimension of no more than about 100 nm.

116. (Withdrawn) A method as in claim 109, wherein the plurality of aggregates comprises at least seven metal particles.

117. (Withdrawn) A method as in claim 107, wherein the surface enhanced radiation has an enhancement factor of at least  $10^{10}$ .

118-121. (Cancelled)

122. (Withdrawn) The method of claim 188, wherein the act of identifying each of the one or more nucleotides comprises:

providing a sample comprising a rough metal film including a plurality of protrusions and indentations;

absorbing the one or more nucleotides on a surface of the film;

exposing the sample to electromagnetic radiation to cause Raman scattering; and

obtaining a unique Raman signal attributed to a single nucleotide.

123-124. (Cancelled)

125. (Withdrawn) The method of claim 188, comprising:

sequentially removing the one or more nucleotides from one end of the nucleic acid.

126. (Withdrawn) The method of claim 188, wherein said nucleic acid is attached to a surface.

127. (Cancelled)

128. (Withdrawn) The method of claim 188, wherein said nucleotides are identified by surface enhanced Raman spectroscopy (SERS) and/or surface enhanced resonance Raman spectroscopy (SERRS).

129. (Cancelled)

130. (Withdrawn) The method of claim 188, wherein each nucleotide is attached to a single nanoparticle or a nanoparticle aggregate.

131. (Cancelled)

132. (Withdrawn) The method of claim 128, further comprising exciting said nucleotides with a laser.

133. (Withdrawn) The method of claim 132, wherein a charge coupled device (CCD) camera is used to identify said nucleotides.

134. (Withdrawn) The method of claim 188, further comprising recording the identity of each nucleotide and the time at which each nucleotide is identified.

135. (Withdrawn) The method of claim 188, wherein an exonuclease is used to remove said nucleotides from said nucleic acid.

136-137. (Cancelled)

138. (Withdrawn) The method of claim 188, further comprising, prior to the act of removing one or more nucleotides from the nucleic acid:

obtaining one or more nucleotides that are attached to Raman labels; and  
providing a nucleic acid comprising the labeled nucleotides.

139. (Withdrawn) The method of claim 188, further comprising passing the nucleotides removed from the nucleic acid in a stream.

140-145. (Cancelled)

146. (Withdrawn) The method of claim 188, wherein said nucleotides are removed from said nucleic acid by exonuclease activity.

147. (Withdrawn) The method of claim 146, wherein only one nucleic acid at a time is exposed to exonuclease activity.

148-152. (Cancelled)

153. (Withdrawn) The method of claim 188, comprising:  
moving the nucleotides in a stream packed with nanoparticles.

154. (Cancelled)

155. (Withdrawn) The method of claim 188, further comprising attaching said nucleic acid to a surface.

156. (Withdrawn) The method of claim 188, wherein said nucleic acid is immobilized in a reaction site.

157. (Withdrawn) The method of claim 156, wherein a single nucleic acid is immobilized in said reaction site.

158. (Cancelled)

159. (Withdrawn) The method of claim 153, wherein at least two nanoparticles are cross-linked together.

160. (Withdrawn) The method of claim 153, wherein the nanoparticles comprise gold and/or silver, said nanoparticles between about 10 nm and 20 micrometers in size.

161. (Withdrawn) The method of claim 160, wherein the size of said nanoparticles is selected from the group consisting of about 10 to 50 nm, about 10 to 100 nm, about 10 nm and about 500 nm.

162. (Withdrawn) The method of claim 188, further comprising:  
preparing a nucleic acid comprising labeled nucleotides.

163. (Cancelled)

164. (Withdrawn) The method of claim 189, wherein each type of nucleotide is labeled with a distinguishable Raman label.

165-171. (Cancelled)

172. (Withdrawn) The method of claim 188, wherein each type of nucleotide produces a unique Raman signal.

173-178 (Cancelled)

179. (Withdrawn) The method of claim 188, further comprising:  
attaching each of the one or more nucleotides to at least one nanoparticle.

180. (Withdrawn) The method of claim 179, wherein said at least one nanoparticle comprises a modified surface.

181. (Cancelled)

182. (Withdrawn) The method of claim 179, wherein said nanoparticles comprise gold and/or silver.



183. (Withdrawn) The method of claim 179, wherein each nucleotide is attached to a single nanoparticle or a nanoparticle aggregate.

184-186. (Cancelled)

187. (Withdrawn) The method of claim 179, wherein said nanoparticles are between 10 nm and 20 micrometers in diameter.

188. (Previously Presented) A method for determining a sequence of at least a portion of a DNA or an RNA strand, comprising:

a) fragmenting one or more bases from a DNA or an RNA strand using a nuclease to form a plurality of fragments, each fragment comprising at least one base;  
b) sequentially identifying each of the one or more fragments by Raman spectroscopy;  
and

c) determining the sequence of at least a portion of the DNA or RNA strand based on the sequential identification of each of the one or more fragments.

189. (Previously Presented) The method of claim 188, wherein each fragment is labeled with a Raman label.

190. (Currently Amended) The method of claim 188, wherein the ~~nucleic acid~~ DNA or RNA strand comprises labeled thymine.

191. (Currently Amended) The method of claim 188, wherein the ~~nucleic acid~~ DNA or RNA strand comprises labeled adenine.

192. (Currently Amended) The method of claim 188, wherein the ~~nucleic acid~~ DNA or RNA strand comprises labeled cytosine.

193. (Currently Amended) The method of claim 188, wherein the ~~nucleic acid~~ DNA or RNA strand comprises labeled guanine.

194. (Currently Amended) The method of claim 188, wherein the ~~nucleic acid~~ DNA or RNA strand comprises labeled uracil.

195. (Previously Presented) The method of claim 188, wherein sequentially identifying each of the one or more fragments by Raman spectroscopy comprises sequentially identifying each of the one or more fragments by surface enhanced Raman spectroscopy (SERS) and/or surface enhanced resonance Raman spectroscopy (SERRS).

196. (Withdrawn) The method of claim 179, wherein the act of attaching each of the one or more nucleotides to at least one nanoparticle occurs prior to the act of removing one or more nucleotides from a nucleic acid.

197. (Withdrawn) The method of claim 179, wherein the act of attaching each of the one or more nucleotides to at least one nanoparticle occurs after the act of removing one or more nucleotides from a nucleic acid.

198. (Previously Presented) The method of claim 188, wherein each of the one or more bases is free of an emission-enhancing aid.

199. (Previously Presented) The method of claim 188, wherein the act of sequentially identifying each of the one or more fragments by Raman spectroscopy comprises attaching each fragment to a surface, and identifying each fragment on the surface using Raman spectroscopy.

200. (Previously Presented) The method of claim 199, wherein the surface is the surface of a metal film.

201. (Previously Presented) The method of claim 199, wherein the surface is the surface of a metal particle.

202. (New) The method of claim 188, wherein sequentially identifying by Raman spectroscopy involves analyzing Raman data in which at least one spectral line represents a single nucleotide.